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(54) Title: COMPOSITIONS FOR THE TREATMENT OF PERIPHERAL NEUROPATHIES CONTAINING ANTIDEPRESSANTS AND/OR MONOAMINE OXIDASE INHIBITORS AND/OR VITAMIN B12 AND/OR PRECURSORS OR INDUCERS OF A NEUROTRANSMITTER

(57) Abstract

Methods and compositions for treatment of a patient suffering from a form of peripheral neurophathy are disclosed. The method comprises administering to the patient any one of the following combinations of components: I. A, B and C; II. A and B; III. B and C; IV. A and C, wherein A is an antidepressant or a monoamine oxidase inhibitor, B is vitamin B_{12}, and C is a precursor or inducer of a neurotransmitter, e.g. L-phenylalanine.

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COMPOSITIONS FOR THE TREATMENT OF PERIPHERAL NEUROPATHIES CONTAINING ANTIDEPRESSANTS AND/OR MONOAMINE OXIDASE INHIBITORS AND/OR VITAMIN B12 AND/OR PRECURSORS OR INDUCERS OF A NEUROTRANSMITTER

TECHNICAL FIELD

The present invention relates to the use of a combined medicament in the treatment of various forms of peripheral neuropathy, especially painful neuropathies and diabetic neuropathy, including diabetic amyotrophy, mononeuritis, mononeuritis multiplex, cranial nerve palsies and autonomic neuropathy. The invention also relates to the preparation of medicaments for such treatments.

BACKGROUND OF THE INVENTION AND PRIOR ART

Diabetes mellitus is a metabolic disorder resulting in hyperglycaemia (raised blood sugar), polyuria (increased output of urine) and glycosuria (appearance of sugars (e.g. glucose) in the urine). Diabetes has been recognised as a major disease for centuries. In addition to defective carbohydrate metabolism, it can also lead to altered metabolism of lipids and proteins and patients are at risk of complications from microvascular and macrovascular diseases which are serious and may be fatal.

Insulin dependent diabetes results from failure of the islets of Langerhans (β) cells of the pancreas to produce sufficient insulin. This often arises as a result of auto-immunity directed against islet tissue. Non-insulin-dependent diabetes may in part arise from altered efficiency of insulin receptor signalling (insulin resistance) or from a relative deficiency of insulin.

Detectable diabetic neuropathy occurs in approximately 60% of diabetic patients. Some 20% of diabetic patients show moderate to severe symptoms, the severity is generally thought to be linked to the duration of diabetic symptoms and the level of control using e.g. insulin, or oral hypoglycaemic agents such as the sulphonylureas.

Diabetic neuropathy may be mild, for example taking the form of "burning" or tingling in the feet or numbness and/or loss of vibration sense in the extremities, especially the feet. Moderate to severe symptoms of neuropathy include pain and spasm in the extremities (painful neuropathy with spasm). Diabetic amyotrophy is indicated by pain over the thigh and loss of quadriceps power, sometimes also loss of power in the lower leg resulting in foot drop. Autonomic neuropathy principally affects the nerves supplying the heart and viscera. Mononeuritis is usually caused by a single peripheral nerve palsy.

Other peripheral neuropathies include the following:

- HIV associated neuropathy;
- B_{12}-deficiency associated neuropathy;
- cranial nerve palsies;
- drug-induced neuropathy;
- industrial neuropathy;
- lymphomatous neuropathy;
- myelomatous neuropathy;
- multi-focal motor neuropathy;

- chronic idiopathic sensory neuropathy;
- carcinomatous neuropathy;
- acute pan autonomic neuropathy;
- alcoholic neuropathy;
- compressive neuropathy;
- vasculitic/ischaemic neuropathy;
- mono- and poly- neuropathies.

Both type I (insulin dependent) diabetes and type II (non-insulin dependent) diabetes are associated with neuropathy. Type I diabetes commonly presents in relatively young adults, often with diabetic ketoacidosis, type II diabetes (also know as maturity onset diabetes) often occurs in middle age or in elderly patients. Type II diabetes is particularly associated with the relatively late and severe onset of neuropathy.

Previous treatments for diabetic neuropathy have included tricyclic antidepressants on their own, the antiepileptic drug carbemazepine, and the antiarrythmic drug mexilitene. However these seem only to be mildly effective, and not in all cases. Long term good diabetic control has also shown to be a benefit in the prevention of diabetic neuropathy and in control of the symptoms, presumably controlling the agents which cause the damage to the nerves. There is little indication that long term control of diabetes can reverse symptoms i.e. the damage, once done, appears not to be reversible by treatment of the underlying diabetes.

Recent clinical trials have shown that gamolenic

acid may reduce symptoms, and prevent the progression of abnormalities in nerve conduction studies in diabetic neuropathy.

WO 96/11009 discloses treatment of multiple sclerosis by some of the combinations of components employed in the present invention.

Vitamin B_{12} has been proposed for the treatment of B_{12}-deficiency associated neuropathy.

DISCLOSURE OF THE INVENTION

The present inventor has surprisingly found that a combination of an antidepressant or a monamine oxidase inhibitor (MAOI) with an inducer or a precursor of a neurotransmitter can be effective in the treatment of peripheral neuropathies, and in particular painful neuropathy. The components of this medicament may be presented as a combined preparation for simultaneous, separate or sequential use in the treatment of various peripheral neuropathies. It has also been observed that a parallel or simultaneous administration of vitamin B_{12} treatment, for example orally or by injection, may enhance the therapeutic effect of this combination.

It has also been found that combinations (i) vitamin B_{12} with an inducer or a precursor of a neurotransmitter and (ii) vitamin B_{12} with an antidepressant, are effective in treatment of peripheral neuropathies.

Accordingly, in a first aspect the present invention provides the use of any one of the following components or

combinations of components:

C,

A and B,

A and C,

B and C,

A, B and C,

wherein

A is an antidepressant or a monoamine oxidase inhibiter,

B is vitamin B_{12}, and

C is a precursor or inducer of a neurotransmitter,

in the manufacture of a medicament for the treatment of at least one form of peripheral neuropathy.

In another aspect the invention provides a method of making a medicament for the treatment of a patient suffering from a peripheral neuropathy, comprising admixing any one of the following components:

C,

A and B,

A and C,

B and C,

A, B and C,

wherein

A is an antidepressant or a monoamine oxidase inhibiter,

B is vitamin B_{12}, and

C is a precursor or inducer of a neurotransmitter,

with at least one pharmaceutically acceptable component or

vehicle to prepare a medicament suitable for administration to a patient.

In yet another aspect the invention provides a method of treatment of a patient suffering from a form of peripheral neuropathy, comprising administering to the patient any one of the following combinations of components:

I. A, B and C

II. A and B

III. B and C

IV. A and C

wherein

A is an antidepressant or a monoamine oxidase inhibitor,

B is vitamin B_{12}, and

C is a precursor or inducer of a neurotransmitter,

said components being administered simultaneously or separately, in amounts which in combination have the effect of ameliorating the peripheral neuropathy.

In a further aspect the invention provides a pharmaceutical composition containing as the only pharmaceutically active components vitamin B_{12} and a precursor or inducer of a neurotransmitter.

Treatment may be simultaneous or separate including sequential administration of the components.

In the medicaments of the invention, there may be included at least one pharmaceutically acceptable

component or vehicle such as an incipient, carrier, buffer, stabiliser or other material, as discussed below.

Also provided is a kit or pack containing components A and B, or A and C, or A and B and C, or B and C, wherein component A the components being formulated for simultaneous, separate or sequential delivery in the treatment of peripheral neuropathy. Particularly components A and C may be combined, and component B separate.

The diabetic neuropathy with which the present invention is concerned may be characterised by degeneration of the long nerves (the nerves of the peripheral nervous system) as a result of the metabolic disturbances of diabetes. This can be contrasted with other neurodegenerative disorders such multiple sclerosis, the effects of which are concentrated in the central nervous system. Whilst multiple sclerosis leads to demyelination of the neurons of the central nervous system (that is, degeneration of the myelin sheath which surrounds the neurons), the toxic effects of diabetes occur in the body of the peripheral neuron, possibly due to the toxic effect of metabolites arising through the underlying diabetic disturbance of carbohydrate metabolism, or as a secondary effect of diabetic microvascular degeneration. Whatever the mechanism, the result of the degenerative changes in the body of the peripheral neuron is reduced signal conductivity along the length of the nerve. It is believed that the initial

generation of a signal and the passage of a signal across synapses may not be directly effected by the condition.

In addition to diabetic neuropathies, the present invention is applicable to any and all of peripheral neuropathies, particularly painful neuropathies, including those listed above in the introduction.

Preferred antidepressants for use in the present invention include tricyclic and tetracyclic antidepressants such as lofepramine and selected seritonin re-uptake inhibitors (SSRI). Lofepramine and certain other tricyclic antidepressants also show some monoamine oxidase inhibitor (MAOI) activity. Other suitable antidepressants and MAOIs include mianserin, trimipramine, imipramine, clomipramine, amitriptyline, protriptyline, nortriptyline, fluvoxamine, fluoxetine, maprotiline, sertaline, venlaflaxine, pargyline, triazolopyridine, phenelzine, tranylcypromine, desipramine, moclopemide, dothiepin, dóxepin, paroxetine, oxazine or viloxazine, amongst others.

A neurotransmitter inducer is a component which enhances or triggers production of a neurotransmitter.

A preferred neurotransmitter precursor for use in the present invention is L-phenylalanine (LPA). However L-tryptophan may also find use in the present invention.

Other amino acids such as L-tyrosine or other compounds such as tyramine may also find use in the present invention as a neurotransmitter, inducer or precursor.

Compounds may be provided as a metabolite of a precursor. For example, L-phenylalanine may be provided as a metabolite of aspartame.

If the combination for treatment includes vitamin B_{12}, this may be in the form of cyanocobalamin or hydroxycobalamin, to be administered orally or intramuscularly.

The compositions provided herein may comprise an antidepressant or a monoamine oxidase inhibitor (MAOI) and a neurotransmitter precursor or inducer, or any other combination of components disclosed herein, as combined (simultaneous or sequential) actives. However, compounds may be employed which mimic a given active in improving diagnostic status and/or ameliorating one or more symptoms of diabetic neuropathy (mimetics). Such compounds and their use are within the scope of the present invention. Also within the scope of the present invention are derivatives or analogues of the antidepressant or MAOI which retain the antidepressant or MAOI activity, respectively.

In accordance with the present invention, compositions provided may be administered to individuals. Administration is preferably in a "therapeutically effective amount", this being sufficient to show benefit to a patient. Such benefit may be at least amelioration of at least one symptom. The actual amount administered, and rate and time-course of administration, will depend on the nature and severity of what is being treated.

Prescription of treatment, eg decisions on dosage etc, is within the responsibility of general practitioners and other medical doctors. Dose regimens for the MAOIs and antidepressants may be within the range used for the treatment of depression (for which the standard starting dose of lofepramine is 140mg per day). With the proviso that the prescribing physician will be able to decide suitable and safe dosage levels, a possible range for administration of antidepressants is 10-210mg per day, although 50-70mg per day may be suitable. For the neurotransmitter precursors or inducers, a range of 100mg to 5g per day, preferably 500-2000mg/d (mg per day) may be employed, the dose increasing in proportion to the level of antidepressant or MAOI employed.

As an example, a 70mg dose of lofepramine may be combined with 500mg of L-phenylalanine given in the morning, this being supplemented with a further 500mg of L-phenylalanine given in the afternoon.

Where vitamin B_{12} is co-administered, the amounts may be those generally recommended for daily intake of the vitamin or may be greater than that recommended as average daily intake. The preferred average dosage range for vitamin B_{12} in the invention is from 1mg every 3 months up to 1mg every 3 days. When symptoms are severe, this may be 1mg intramuscular hydroxycobalamin per week in an 8-10 week course at the start of treatment, perhaps reduced to 1mg every 10 days as treatment progresses. The desired dosage level of vitamin B_{12} may conveniently be given by

weekly intramuscular injection, but doses ranging from 5μg to 10mg may be given daily orally.

Pharmaceutical compositions according to the present invention, and for use in accordance with the present invention, may comprise, in addition to active ingredient, a pharmaceutically acceptable excipient, carrier, buffer, stabiliser or other materials well known to those skilled in the art. Such materials should be non-toxic and should not interfere with the efficacy of the active ingredient. The precise nature of the carrier or other material will depend on the route of administration, which may be oral, or by injection, e.g. cutaneous, subcutaneous or intravenous.

Pharmaceutical compositions for oral administration may be in tablet, capsule, powder or liquid form. A tablet may comprise a solid carrier such as gelatin or an adjuvant. Liquid pharmaceutical compositions generally comprise a liquid carrier such as water, petroleum, animal or vegetable oils, mineral oil or synthetic oil. Physiological saline solution, dextrose or other saccharide solution or glycols such as ethylene glycol, propylene glycol or polyethylene glycol may be included.

For intravenous, cutaneous or subcutaneous injection, or injection at the site of affliction, the active ingredient will be in the form of a parenterally acceptable aqueous solution which is pyrogen-free and has suitable pH, isotonicity and stability. Those of relevant skill in the art are well able to prepare suitable

solutions using, for example, isotonic vehicles such as Sodium Chloride Injection, Ringer's Injection, Lactated Ringer's Injection. Preservatives, stabilisers, buffers, antioxidants and/or other additives may be included, as required. L-tryptophan and L-phenylalanine are available in 500mg tablets.

A combined oral preparation in single tablet form, containing all these components A, B and C, or for example components B and C, is feasible. Alternatively, a treatment pack may contain the components separately.

EXAMPLES

Case #1

A 48 year old male, diagnosed non-insulin dependent diabetic when aged 28, showed symptoms of diabetic neuropathy which commenced approximately 8 years ago. The onset of neuropathy was thought to be due to poor control of diabetes. Neuropathic symptoms increased in severity over several years with development of severe diabetic neuropathy including diabetic amyotrophy, painful neuropathy with spasm, diabetic autonomic neuropathy and decreased sensation in the extremities, with numbing and loss of vibration sense. Electromyography confirmed the diagnosis of diabetic neuropathy.

Treatment with tricyclic antidepressants and carbemazepine was ineffective. An improvement in control of the patient's diabetes also did not significantly affect his severe symptoms.

A regime of 70mg lofepramine and 500mg LPA, each administered with informed consent twice daily, with weekly 1mg vitamin B_{12} injections, significantly improved reported symptoms within 12 hours. Almost complete clinical resolution of clinical signs and symptoms had occurred after one week of combined therapy.

Long term maintenance of diabetic neuropathic remission has required continued treatment, for this patient.

Case #2

A 55 year old male with non-insulin dependent diabetes with very severe diabetic neuropathy, including diabetic amyotrophy and bedbound, resistant to current therapies, was commenced on vitamin B_{12} injections (1mg at two-week intervals) and L-phenylalanine (as a metabolite of aspartame) 500mg twice a day.

Benefit in amyotrophy was noted within 3 hours of commencement of treatment. The subsequent addition of lofepramine 70 mg twice daily produced a further improvement. Within 3 weeks his diabetic amyotrophy was considerably improved.

Case #3

This case studied here is of the same 48 year old male with diabetic neuropathy as in case #1, but after the original observation in case #1. The patient was subsequently continued on the same vitamin B_{12} injections

and phenylalanine (500mg twice daily) only. He continued to benefit from his therapy whilst on these two drugs only, for approximately two months, and then required the recommencement of lofepramine to maintain good effect clinically.

Case #4

A 72 year old male with vitamin B_{12} neuropathy and mild alcoholic neuropathy was studied.

Clinical progress with vitamin B_{12} injections alone was insignificant. The addition of lofepramine to the medication enabled the patient to retain his balance, lose his painful neuropathy, and within 3 days ambulate almost normally. Previously he required the assistance of another person to walk.

Case #5

A 76 year old female with non-insulin dependent diabetes for 15 years with reasonable control, developed peripheral painful diabetic neuropathy of two months duration. She was commenced with vitamin B_{12} 1mg weekly, L-phenylalanine 500mg twice daily and lofepramine 35mg twice daily (reduced dosage because of age) with a very good response within 48-72 hours. All symptoms had disappeared. The treatment was stopped six weeks after the commencement of the therapy and there has been no recurrence in the two months to the time of report of this case.

Case #6

A 50 year old male who had diabetes for 15 years more recently requiring insulin therapy, developed peripheral painful diabetic neuropathy which had become severe, he was commenced on vitamin B_{12} 1mg intramuscular weekly, lofepramine 70mg twice daily and L-phenylalanine 500mg twice daily. He had a good response within the first two weeks. After that period treatment was stopped and he had no recurrence of symptoms and there were no side effects detected.

Case #7

A 59 year old male with peripheral diabetic neuropathy and impotence of 3 years duration becoming increasingly severe over three months period prior to therapy. He was commenced on weekly vitamin B_{12} 1mg intramuscular, lofepramine 70mg twice daily and L-phenylalanine 500mg twice daily. He had a good immediate response within the first two weeks with no side effects. He continues with his treatment at the time of report of this case.

Case #8

A male in his fourth decade had mild painful peripheral alcoholic neuropathy of six months duration with increasing severity over the past two months. In addition he complained of a compressive neuropathy involving the C6 nerve root. He was commenced on vitamin

B_{12} orally 200μg daily and L-phenylalanine 500mg twice daily with a considerable reduction in symptomatology whilst on therapy.

Case #9

A male in his fifth decade was HIV positive and complained of moderate peripheral neuropathy including painful neuropathy. He also had mild diabetes of short duration but clinically his neuropathy was diagnosed as that related to HIV. He had been previously commenced on amitriptyline 75 mg daily with some mild beneficial effects. He was additionally commenced on L-phenylalanine 500 mg twice daily, whereafter he reported an approximate further 50% improvement in the symptoms of his painful neuropathy.

Case #10

A female in her sixth decade had severe diabetic peripheral neuropathy and resultant Charcot foot joints. She was initially placed on tricyclic anti-depressants in the form of dothiepin 150 mg once daily with a mild beneficial effect. The subsequent addition of vitamin B_{12} injections 1mg weekly, resulted in improvement in painful symptomatology. Vibration sense was also improved. Further clinical benefit was gained by the addition of L-phenylalanine 500 mg twice daily. Vibration sense initially could not be detected at a level below the knee. During therapy the level at which vibration sense which

could be detected was at the level of the medial malleolus. Her pain has subsided and she has noted no further progression in the damage to her joints to date of reporting of this case.

It will be apparent to those skilled in the art that variations and modifications to the specific embodiments disclosed herein may be made without departing from the scope of the invention.

CLAIMS

1. Use of any one of the following components or combinations of components:

C,

A and B,

A and C,

B and C,

A, B and C,

wherein

A is an antidepressant or a monoamine oxidase inhibiter,

B is vitamin B_{12}, and

C is a precursor or inducer of a neurotransmitter,

in the manufacture of a medicament for the treatment of at least one form of peripheral neuropathy.

2. Use according to claim 1, wherein the peripheral neuropathy is a diabetic neuropathy.

3. Use according to claim 1 or 2, wherein the peripheral neuropathy is a painful neuropathy.

4. Use according to claim 1, 2 or 3, wherein A is a tricyclic or tetracyclic antidepressant or a selected seritonin re-uptake inhibitor.

5. Use according to claim 4, wherein A is lofepramine.

6. Use according to any one of claims 1 to 5, wherein B is in the form of cyanocobalamin or hydroxycobalamin.

7. Use according to any one of claims 1 to 6, wherein C is L-phenylalanine, L-tyrosine, L-tryptophan or tyramine.

8. Method of making a medicament for the treatment of a patient suffering from a peripheral neuropathy, comprising admixing any one of the following components or combinations of components:

C,

A and B,

A and C,

B and C,

A, B and C,

wherein

A is an antidepressant or a monoamine oxidase inhibiter,

B is vitamin B_{12}, and

C is a precursor or inducer of a neurotransmitter,

with at least one pharmaceutically acceptable component or vehicle to prepare a medicament suitable for administration to a patient.

9. Method according to claim 8, wherein said medicament contains one of the following combinations of components:

A, B and C,

A and B,

B and C,

A and C,

in a form or forms suitable for simultaneous or separate administration.

10. Method according to claim 8 or 9, wherein the neuropathy is a painful neuropathy.

11. Method according to claim 8, 9 or 10, wherein the neuropathy is diabetic neuropathy.

12. Method according to any one of claims 8 to 11, wherein A is a tricyclic or tetracyclic antidepressant or a selected seritonin re-uptake inhibitor.

13. Method according to claim 12, wherein A is lofepramine.

14. Method according to any one of claims 8 to 13, wherein B is in the form of cyanocobalamin or hydroxycobalamin.

15. Method according to any one of claims 8 to 14, wherein C is L-phenylalanine, L-tyrosine, L-tryptophan or tyramine.

16. Method of treatment of a patient suffering from a form of peripheral neuropathy, comprising administering to the patient any one of the following combinations of components:

I. A, B and C

II. A and B

III. B and C

IV. A and C

wherein

A is an antidepressant or a monoamine oxidase inhibitor,

B is vitamin B_{12}, and

C is a precursor or inducer of a neurotransmitter,

said components being administered simultaneously or

separately, in amounts which in combination have the effect of ameliorating the peripheral neuropathy.

17. Method according to claim 16 wherein the neuropathy is a painful neuropathy.

18. Method according to claim 16 and 17 wherein the neuropathy is diabetic neuropathy.

19. Method according to any one of claims 16 to 18, wherein A is a tricyclic or tetracyclic antidepressant or a selected seritonin re-uptake inhibitor.

20. Method according to claim 19, wherein A is lofepramine.

21. Method according to any one of claims 16 to 20, wherein B is in the form of cyanocobalamin or hydroxycobalamin.

22. Method according to any one of claims 16 to 21, wherein C is L-phenylalanine, L-tyrosine, L-tryptophan or tyramine.

23. A pharmaceutical composition containing as the only pharmaceutically active components vitamin B_{12} and a precursor or inducer of a neurotransmitter.

24. A pharmaceutical composition according to claim 23 wherein vitamin B_{12} is in the form of cyanocobalamin or hydroxycobalamin.

25. A pharmaceutical composition according to claim 23 or 24, wherein the precursor or inducer of a neurotransmitter is L-phenylalanine, L-tyrosine, L-tryptophan or tyramine.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 97/01822

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K45/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 11009 A (LODER CARI) 18 April 1996 cited in the application see abstract	1-25
A	OKADA S ET AL: "EFFECT OF METHYLCOBALAMIN ON DIMINISHED MOTOR NERVE CONDUCTION VELOCITY IN THE TIBIAL NERVE OF POORLY CONTROLLED DIABETICS" CLIN TRIALS J, 22 (6). 1985 (RECD. 1986). 534-536., XP002047637 see abstract	1-25
A	SIMON K.H.: "ZUR BEHANDLUNG THERAPIERESISTENTER SCHMERZZUSTANDE MIT HYDROXOCOBALAMIN" MED.MSCHR., 1974, 28/10 (466-468), GERMANY, WEST, XP002047638 see page 468, column 2	1-25

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
20 November 1997	16.12.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Leherte, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 97/01822

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CALANCA A.: "HYDROXYTRYPTOPHANE (OXITRIPTAN) EN ASSOCIATION AVEC LES ANTIDEPRESSEURS CLASSIQUES: UNE ULTERIEURE POSSIBILITE THERAPEUTIQUE" SCHWEIZ. RUNDSCH. MED. PRAX., 1988, 77/34 SUPPL. (47-50), SWITZERLAND, XP002047639 see abstract ----	1-25

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 97/01822

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 16-22 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 97/01822

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